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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/445,517	12/06/1999	BRADFORD J DUFT	235/013 US	1018

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EXAMINER	
DEVI, SARVAMANGALA J N	
ART UNIT	PAPER NUMBER
1645	13

DATE MAILED: 06/05/2002

9/5/02

Please find below and/or attached an Office communication concerning this application or proceeding.

rec'd from amylin 6/21/02 BJL

Office Action Summary

Application No.	Applicant(s)
09/445,517	Duft et al.
Examiner	**Art Unit**
S. Devi, Ph.D.	1645

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Oct 23, 2001*

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-15* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *12.*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicants' Amendment and Response

1) Acknowledgment is made of Applicants' amendment filed 08/24/01 (paper no. 9) and Applicants' supplemental response filed 10/23/01 (paper no. 11) in response to the non-final rejection mailed 04/20/01 (paper no. 6).

Status of Claims

2) No claims have been amended.

Claims 1-15 are pending and are under examination.

Prior Citation of Title 35 Sections

3) The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior Office Action.

Prior Citation of References

4) The references cited or used as prior art in support of one or more rejections in the instant Office Action and not included on an attached form PTO-892 or form PTO-1449 have been previously cited and made of record.

Information Disclosure Statements

5) Acknowledgment is made of Applicant's Information Disclosure Statement filed 06/08/01 and 04/23/02 (paper no. 7 and 12). Except for those references that have already been cited on a previous PTO-892, the information referred to therein has been considered and a signed copy is attached to this Office Action (paper no. 13).

Objection(s) Withdrawn

6) The objection to the specification made in paragraph 4 of the Office Action mailed 08/04/00 (paper no. 3) with regard to the missing abstract, is withdrawn. Applicants request that a copy of the published abstract from the priority application, PCT/US98/11753, be used in this case. Accordingly, a copy of the published abstract from WO 98/55144 has been made of record as page number 52 in the instant application.

7) The objection to the specification made in paragraph 5 of the Office Action mailed 08/04/00 (paper no. 3) is withdrawn in light of Applicants' amendments to the specification.

Rejection(s) Withdrawn

8) The rejection of claims 1-5 made in paragraph 14 of the Office Action mailed 04/20/01 (paper no. 6) under 35 U.S.C § 103(a) as being unpatentable over Arnelo *et al.* (Arnelo *et al. Am. J. Physiol.* 271: 6 pt 2: R1654-R1659, December 1996) (Arnelo *et al.* I), or Arnelo *et al.* (*Scand. J. Gastroenterol.* 31: 83-89, January 1996) (Arnelo *et al.* II), is withdrawn. Applicants are asked to note the new rejection(s) made below, wherein the applied reference(s) taught administration of pramlintide to humans.

9) The rejection of claims 6-8 made in paragraph 15 of the Office Action mailed 04/20/01 (paper no. 6) under 35 U.S.C § 103(a) as being unpatentable over Arnelo *et al.* (Arnelo *et al. Am. J. Physiol.* 271: 6 pt 2: R1654-R1659, December 1996) (Arnelo *et al.* I), or Arnelo *et al.* (*Scand. J. Gastroenterol.* 31: 83-89, January 1996) (Arnelo *et al.* II) as applied to claim 5, and further in view of Bennett *et al.* (US 5,955,443), is withdrawn. Applicants are asked to note the new rejection(s) made below, wherein the applied reference(s) taught administration of pramlintide to humans.

10) The rejection of claims 1 and 5 made in paragraph 17 of the Office Action mailed 04/20/01 (paper no. 3) under 35 U.S.C § 103 (a) as being unpatentable over Morley *et al.* (*Am. J. Physiol.* 267: R178-R184, 1994) (Morley *et al.*, 1994), is withdrawn. Applicants are asked to note the new rejection(s) made below, wherein the applied reference(s) taught administration of prmalintide to humans.

11) The rejection of claims 11-15 made in paragraph 13 of the Office Action mailed 08/04/00 (paper no. 3) and maintained on page 3 of the Office Action mailed 04/20/01 (paper no. 6) under 35 U.S.C § 103(a) as being unpatentable over Kolterman *et al.* (*Diabetes Care* 18: 1179-1182, August 1995) (Kolterman *et al.*, 1995) in view of Rosenbloom *et al.* (*Am. J. Dis. Child.* 131: 881-885, 1977), Rink *et al.* (WO 92/20367) (Rink *et al.*, '367) and Morley *et al.* (*Am. J. Physiol.* 267: R178-R184, 1994) (Morley *et al.*, 1994), is withdrawn. Applicants are asked to note the new and/or modified rejection(s) made below.

12) The rejection of claims 1-10 made in paragraph 16 of the Office Action mailed 04/20/01 (paper no. 6) under 35 U.S.C § 103 (a) as being unpatentable over Kolterman *et al.* (WO

96/40220, already of record) (Kolterman *et al.* II) in view of Meglasson (US 5,134,164), is withdrawn. Applicants are asked to note the new and/or modified rejection made below.

The Young Declaration

13) Applicants contend that the Young Declaration provides data showing that continuous administration of amylin resulted in reduced body weight compared to the controls in spite of the fact that there was no overall reduction in long term food intake. The Declaration states that the effects of amylin to ameliorate weight gain are not predicted by, or obligatorily linked to, an effect on food intake.

The contents of the Declaration have been considered, but are not persuasive. The scope of the instant claims, as drafted currently, does not exclude reduction of weight gain by amylin or amylin agonist by way of decreasing the quantity or frequency of food intake. Instant claims encompass a method of treating obesity comprising continuous or discontinuous administration of amylin or amylin agonist, irrespective of the mechanism by which amylin acts. Furthermore, the art at the time reflected that a composition comprising amylin or amylin agonist suppresses or reduces food intake, controls appetite and controls body weight in a mammal (see claims). For instance, Rink *et al.* (US 5,739,106 issued to Amylin Pharmaceuticals) taught the reduction of food intake as an amylin agonist activity (see lines 1-5 in column 15).

Applicants' Arguments on Applied Prior Art

14) Applicants' arguments with respect to instant claims have been considered, but are moot in view of the new/modified grounds of the new grounds of rejection.

Applicants cite case law and contend that Kolterman *et al.* (1995) focus on a narrow time frame of five hours over which time it would be not be possible to gauge meaningful insulin-induced weight control. Applicants contend that Kolterman *et al.* at page 1181, column 2, last paragraph, recognize this by the statement: "[I]t needs to be demonstrated that similar results can be achieved throughout the entire day ...". Applicants interpret Kolterman's statement: "This latter finding is consistent with recent observations in humans (9), but contradicts earlier observations in animal models (10-11)", as allegedly teaching that amylin actions in rodent models are not necessarily indicative of amylin activities in humans. Because of these reasons, Applicants conclude that Kolterman is an unlikely reference to be combined with any other that

pertains to the issue of weight gain.

In response, the Kolterman's (1995) method of administration of amylin or amylin agonist to a insulin-taking **human** subject meets the Applicants' method of administration of amylin or amylin agonist. The instantly claimed method is not limited to a method of administering amylin or amylin agonist for a period that exceeds five hours. The length of amylin administration is not recited as a limitation in the instant claims. The Kolterman's method was carried out in humans as opposed to animals. Thus, there is no need to apply Koltermans' acute findings to humans and therefore, Kolterman's alleged teaching that amylin actions in rodent models are not necessarily indicative of amylin activities humans is irrelevant. The reference of Kolterman's (1995) has now been replaced with a reference that teaches subcutaneous administration of pramlintide for weeks. The various prior art references applied in the rejections made below, all teaching the administration of pramlintide to humans, clearly indicate that the anti-gastric emptying and anorectic (food intake suppressing) actions of amylin seen in animal models were also noticed or reproduced in humans. That a method of administration of amylin or amylin agonist to an insulin-taking **human** subject inherently and concomitantly results in weight loss is evident from Thompson *et al.* (May, 1997), which taught an identical method of subcutaneous administration of pramlintide, an analog of human amylin, to humans on insulin for a period of weeks. See below.

Applicants contend that "by the time the present application was filed, amylin and amylin agonists had never before been used or suggested to treat obesity in humans". Applicants state that studies by this time urged a different course of action, i.e., the use of amylin antagonists to treat obesity as described in US patents 5,280,014 and US 5,364,841. With this, Applicants allege that the Office has failed to take into account of the whole of the art as it existed at the time of filing. In response, a review of the prosecution record in the instant case indicates that the Office first applied US patents '014 and '841 in a rejection, under 35 U.S.C. § 102, of unamended claims 1 and 2 (see page 4 of the Office Action mailed 08/04/00), since the two patents taught a method of treating obesity by administering to a subject an effective amount of CGRP 8-37, an ***amylin agonist***. Given this, one skilled in the art would have been motivated to make use of amylin agonists, perhaps at different doses or by different routes, to treat body

weight, particularly since several published reports at the time had already taught an appetite suppressing or anorexia-causing role for amylin. Since CGRP 8-37 is also described in the patents to have partial amylin antagonistic activities, the rejections were later withdrawn. Furthermore, the disclosure of Rink *et al.* (US 5,739,106) issued to Amylin Pharmaceuticals and the reference of Thompson *et al.* (May, 1997) are *prima facie* evidence that the teachings of US patents '014 and '841 did **not** deter those skilled in the art from using amylin or amylin agonists, including pramlintide, in a method for suppressing food intake, a method for controlling appetite and/or a method for controlling body weight in a mammal. Furthermore, when one takes into consideration the peripheral anorectic effects of amylin as taught by Edwards *et al.* or Frishman *et al.*, the conclusive showing by Morley *et al.* (1993) that amylin is a peripheral anorectic peptide, the anti-gastric emptying effects of amylin or pramlintide as demonstrated by MacDonald *et al.*, Kong *et al.* and the anti-hyperglycemic effects of pramlintide as taught by Kolterman *et al.* ('098), together with the express suggestion in the art that anorectic and anti-gastric emptying agents are desirable as anti-obesity agents as taught by Frishman *et al.* or Weintraub *et al.*, it can hardly be argued that the instant claims are not *prima facie* obvious. The reference of Thompson *et al.* (May, 1997) is *prima facie* evidence that pramlintide is therapeutic not only against diabetes, but against weight gain (obesity) concomitantly.

Applicants then contend that Rink (US 5,656,590) describes methods of treating anorexic patients by administering an amylin or an amylin analogue to increase weight, not lose weight. However, it should be noted that Applicants themselves acknowledge within the instant specification that several publications in the art have reported on the anorexia-causing ability of amylin. See the paragraph bridging pages 9 and 10 of the instant specification. Furthermore, the disclosure of Rink *et al.* (US 5,739,106) issued to Amylin Pharmaceuticals is *prima facie* evidence that the teachings of the patent '590 did not deter those skilled in the art from making use of the anorexia-causing of amylin and amylin agonists, including pramlintide, in a method for suppressing food intake, a method for controlling appetite and/or a method for controlling body weight in a mammal. Additionally, the reference of Thompson *et al.* (May, 1997), thus far undisclosed to the Office under the requirement of 37 C.F.R 1.56, also provides *prima facie* evidence that pramlintide at an optimal dose does decrease body weight in humans in addition to

treating diabetes.

With regard to Applicants' remarks on the issuance of the US patent 6,274,608, it should be noted that the prosecution of one application does not have to duplicate that of a another application. Each case is individually examined and prosecuted on its own merits. A patent application is issued based on the facts and evidence of record in that application. The Office's conclusion on the lack of enablement for a method of "preventing" obesity in the instant case is based on the evidence of record or lack thereof, in the instant application.

Rejection(s) Maintained

15) The provisional rejection of instant claims made in paragraph 13 of the Office Action mailed 08/04/00 (paper no. 3) under the judicially created doctrine of obviousness-type double patenting as being unpatentable over the claims of the co-pending application, SN 09/870,762, is maintained for reasons set forth therein.

Applicants request clarification as to the pending claims that are included in the rejection under the judicially created doctrine of obviousness-type double patenting. In response, instant claims 1-10 stand rejected under the judicially created doctrine of obviousness-type double patenting over claims 1-6 of the co-pending application, SN 09/870,762. It is noted that Applicants request the Office to hold this matter in abeyance until the time of issuance of notification of allowable subject matter.

16) The rejection of claims 1-10 made in paragraph 6 of the Office Action mailed 08/04/00 (paper no. 3) and maintained on page 3 of the Office Action mailed 04/20/01 (paper no. 6) under 35 U.S.C § 112, first paragraph, as being non-enabled with regard to the scope, is maintained for reasons set forth therein.

Applicants contend that the ability to prevent an escalation from one degree of obesity to a severe degree of obesity with a pharmaceutical agent both treats an existing obese condition and prevents exacerbated or further obesity. Applicants state that it is understood that use of such an agent provides the ability to prevent obesity in one who is in danger of manifesting the disease. Applicants urge that the instant specification provides complete support for both treating and preventing obesity and the treatment of patients by lowering body weight and the prevention of body weight increase. Applicants argue that the U.S. Patent and Trademark Office

has issued many patents over the years that contain claims to methods for "treating and preventing" various diseases and provide an example of such a patent. Applicants allege that the Office has advanced no evidence in support of *Wands* analysis, yet acknowledge that the Office has provided the discussion by providing the definition of the term "prevent" from *Webster's II New Riverside University Dictionary*. Applicants cite case law and argue that a specification disclosure must be taken as in compliance with the enabling requirement of the 112, first paragraph, unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

Applicants' arguments have been carefully considered, but are non-persuasive. It should be noted that instant claims are not directed to a method of preventing an escalation from one degree of obesity to a severe degree of obesity with a pharmaceutical agent, or to a method of preventing exacerbated or further obesity. While the specification provides a definition for "treating" obesity, the specification does not provide a definition of "preventing" obesity. In the absence of a closed definition in the instant specification, the Office is to interpret claim limitations broadly. Consistent with what is disclosed in the art, the instant specification indicates that obesity or adiposity is a "chronic disease" (see line 19 on page 9). The instant specification teaches that people inheriting genetic traits are prone to becoming obese regardless of their efforts to combat the condition. See page 10, last paragraph. Instant claims, as drafted currently, encompass prevention of all types of obesity: morbid obesity; genetic obesity; acquired obesity; diabetes-related obesity; obesity due to any metabolic or endocrine disorders etc., the cause of which is multifactorial. The art, in general, reflects that total prevention of obesity, for example, in a morbidly or non-morbidly obese human subject, is difficult and depends on multiple factors, including family genetics, eating habits, behavioral patterns, underlying metabolic or endocrine conditions etc., Transient reduction in body weight may be equivalent to treatment, but not to "prevention" of obesity. The specification lacks evidence showing that a chronic and stubborn condition, obesity, is "prevented" by continuous or discontinuous administration of an amylin or amylin agonist. While there is evidence within the instant specification that pramlintide reduces body weight in patients with diabetes-associated obesity for a period of weeks, no evidence is of record showing that pramlintide, or any amylin, amylin

agonist or amylin agonist analogue "prevents" any type of obesity mentioned above. As set forth in paragraph 6 of the Office Action mailed 08/04/00 (paper no. 3), the *Webster's II New Riverside University Dictionary* defines the term "prevent" as "to keep from happening". There is neither any evidence within the instant specification, nor is there any certainty that administration of amylin, amylin agonist or amylin agonist analogue as claimed, would "keep obesity from happening". Furthermore, amylin, amylin agonists or amylin agonist analogues broadly encompass a myriad of compounds, including human, non-human, synthetic and non-synthetic amylins, amylin agonists and amylin agonist analogues, and non-amylin compounds, such as, calcitonin, CGRP and analogue thereof etc., Examples in the instant specification show that the only amylin species, amylin agonist species or amylin agonist analogue species that showed reduction in body weight is pramlintide. The method of treatment has been demonstrated exclusively in diabetic patients. However, there is no evidence that the complex clinical condition, obesity, in diabetic or non-diabetic population is "prevented" by pramlintide or any other amylin agonist. The full scope of the claims is not commensurate in scope with the evidence or the enabling disclosure. Due to the lack of evidence, the lack of specific guidance as to how to 'prevent' the complex disease of obesity using amylin or amylin agonist, the lack of predictability in the art with regard to the prevention of obesity, the absence of working examples demonstrating that obesity can be 'prevented' as opposed to treated, the broad scope of the claims and the quantity of experimentation necessary, undue experimentation would have been required by one of ordinary skill in the art to reproducibly practice the full scope of the invention, as claimed currently. The ability to reproducibly practice the full scope of the claimed invention is well outside the realm of routine experimentation. The claims are viewed as being non-enabled with respect to the full scope.

Rejection(s) under Double Patenting

17) The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686

F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970) and *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 C.F.R 1.321(c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 C.F.R 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 C.F.R 3.73(b).

18) Claims 1-10 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 7-14 and 83-85 of the US patent 5,739,106 (Rink, already of record). Although the conflicting claims are not identical, they are not patentably distinct from each other because of the overlapping scope. Instant claims are interpreted in light of the specification. The instant specification defines "treating obesity" as "controlling weight", that is "to control body weight" (see last three lines on page 12). The instant specification also defines "treating" obesity to include the administration of amylin or amylin agonist to include "the inhibition of weight gain and inducing weight loss" and to alleviate "the symptoms or complications" (see last paragraph on page 12). Rink's ('106) method for "control of body weight in a mammal" comprising administering or co-administering an amylin agonist, including calcitonin or ^{25,28,29}pro-h-amylin, encompasses the subject matter of the instant claims. Since the processes of "suppressing food intake in a mammal", "reducing food intake in mammal" and "control of appetite in a mammal" (which includes decreasing appetite) all have a direct effect on "controlling" body weight or on "alleviating" weight gain-related symptoms, Rink's ('106) methods for "reducing food intake in a mammal", "for the control of appetite in a mammal" and "for suppressing food intake in a mammal" encompass the subject matter of the instant claims.

19) Claims 1-10 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-25 of US patent 6,114,304 (Kolterman) in view of Weintraub *et al.* (*Nutrition Rev.* 49: 237-249, 1989) and Robert *et al.* (WO 91/16917). Although the conflicting claims are not identical, they are not patentably distinct from each other, because

of the overlapping scope. Instant claims are interpreted in light of the specification. The instant specification defines "treating" obesity to include "controlling weight", that is "to control body weight" (see last three lines on page 12). The instant specification also defines "treating" obesity to include the administration of amylin or amylin agonist to include "the inhibition of weight gain and inducing weight loss" and to alleviate "the symptoms or complications" (see last paragraph on page 12). That Kolterman's ('304) method of "delaying gastric emptying in a mammal" comprising administering a therapeutically effective amount of an amylin, amylin agonist, i.e., amylin agonist analogue, including ^{25,28,29}pro-h-amylin, encompasses the subject matter of the instant claims, is implicit in light of what is known in the art. That the induction of slowing or delaying of gastric emptying has a direct therapeutic effect on the clinical condition of obesity is well known in the art. For instance, Robert *et al.* demonstrated that a gastric emptying-retarding compound also served as an anti-obesity agent by retaining the food in the stomach of the treated individuals for prolonged periods of time, thus causing no desire to eat, thereby causing weight loss. See page 2, lines 24-26 of Robert *et al.* Weintraub *et al.* expressly taught, slowing of gastric emptying by increasing gastric distension to inhibit food intake, as an approach for treating obesity (see title; and page 43, left column, second full paragraph). Given the Robert's express teaching that a gastric emptying-retarding compound also served as an anti-obesity agent by retaining the food in the stomach of the treated individuals for prolonged periods of time, thus causing no desire to eat, thereby causing weight loss, it would have been obvious to one of ordinary skill in the art at the time the invention was made to use Kolterman's ('304) method comprising administering amylin, an amylin agonist analogue, or an amylin agonist compound, such as, ^{25,28,29}pro-h-amylin, to a human subject, for treating obesity to produce the instantly claimed method, with a reasonable expectation of success, because Weintraub *et al.* expressly teach slowing of gastric emptying as an approach for treating obesity.

Rejection(s) under 35 U.S.C. § 112, Second Paragraph

20) The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude one or more claims particularly pointing out and distinctly claiming the subject matter which the Applicant regards as his/her invention.

21) Claims 1-15 are rejected under 35 U.S.C § 112, second paragraph, as being indefinite for

failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

(a) Claims 1 and 11 are vague and indefinite in the recitation: "an effective amount of an amylin" (see line 2), because the term "effective" is a relative term which renders the claim indefinite. The term "effective" is not specifically defined by the claim, the specification does not provide a standard for ascertaining the requisite degree of effectiveness, and one of ordinary skill in the art would not be able to reasonably envisage the scope of the invention. Whether or not the recited 'amount' encompasses therapeutically effective amount, pharmacologically effective amount, prophylactically effective amount, or immunologically effective amount is not understood. Clarification/correction is requested.

(b) Claim 2-10 and 12-15, which depend directly or indirectly from claim 1 and claim 11 respectively, are also rejected under 35 U.S.C. § 112, second paragraph, as being indefinite, because of the indefiniteness identified above in the base claim.

Rejection(s) under 35 U.S.C. § 102

22) The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> **(a)** the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
> **(b)** the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

23) Claims 1-14 are rejected under 35 U.S.C § 102(a) as being anticipated by Thompson *et al.* (*Diabetes* 46: Suppl. 1, page 30A, 0116, 02 May 1997) (Thompson *et al.* May, 1997).

Thompson *et al.* (May, 1997) taught a method of subcutaneous administration of pramlintide, i.e., ^{25,28,29}pro-h-amylin, an analog of human amylin, i.e., an amylin agonist, to patients with type II diabetes requiring insulin, at a dose of 30 or 60 micrograms QID (i.e., four times a day) or TID (i.e., three times a day) for a period of four weeks. The method carried out at a pramlintide dose of 60 micrograms TID or QID not only improved glycaemic control in these patients, but also decreased body weight (see abstract) and therefore, served as a method of treating obesity.

Claims 1-14 are anticipated by Thompson *et al.* (May, 1997).

24) Claims 1-3 and 11-15 are rejected under 35 U.S.C § 102(b) as being anticipated by MacDonald *et al.* (*Diaetologia* 38: Suppl. 1, A118, August 1995, Applicants' IDS) as evidenced by Robert *et al.* (WO 91/16917).

MacDonald *et al.* teach the intravenous infusion of 125 micrograms of human amylin analogue or amylin agonist, AC137, to human subjects with insulin-dependent diabetes mellitus or IDDM who are on insulin. The method induced delayed gastric emptying to such an extent that t50 values could not be calculated for solid or liquid meal components (see abstract).

That the prior art method necessarily serves as a method of treating obesity, i.e., "controlling weight for cosmetic purposes in humans, that is to control body weight to improve bodily appearance", or preventing the "onset of symptoms or complications, alleviating the symptoms or complications", is inherent from the teachings of MacDonald *et al.* in light of what is well known in the art. It is inherently taught that by significantly delaying gastric emptying in the treated patients, the pramlintide used in MacDonald's method necessarily induces weight-controlling or weight-reducing effects, since it is well known in the art that anti-gastric emptying agents also serve as weight-reducing agents. For instance, Robert *et al.* demonstrated that a gastric emptying-retarding compound also serves as an anti-obesity agent by retaining the food in the stomach of the treated individuals for prolonged periods of time, thus causing no desire to eat, thereby causing weight loss. See page 2, lines 24-26 of Robert *et al.*

The teachings of MacDonald *et al.* anticipate the instant claims. Robert *et al.* is **not** used as a secondary reference in combination with MacDonald *et al.*, but rather is used to show that every element of the claimed subject matter is disclosed by MacDonald *et al.* See *In re Samour* 197 USPQ 1 (CCPA 1978).

Claims 1-3 and 11-15 are anticipated by MacDonald *et al.*

25). Claims 1-6 and 11-15 are rejected under 35 U.S.C § 102(a) as being anticipated by Thompson *et al.* (*Diabetes* 46: 632-636, April 1997, already of record) (Thompson *et al.*, April, 1997) as evidenced by Guthrie *et al.* (US 4,443,619).

It is noted that the instant specification defines "treating" obesity as follows (see page 12):

> ..... the management and care of a patient for the purpose of combating the disease, condition or disorder, and includes the administration of an amylin or an amylin agonist to prevent the **onset of symptoms or complications, alleviating the symptoms** or **complications**, or eliminating the disease condition or disorder. Treating obesity therefor includes the inhibition of weight gain and inducing weight loss in patients in need thereof. Additionally, treating obesity is meant to include **controlling weight for cosmetic purposes in humans**, that is **to control body weight to improve bodily appearance**. [Emphasis added].

It is noted that the method claimed in claims 1-6 encompass both insulin-taking and non-insulin-taking human subjects. The methods of claims 1-5 and 11-15 do not require that a specific amount of the recited amylin or amylin agonist be administered. The method of claims 1-3 does not require that the recited amylin or amylin agonist be administered via a specific route. Claims 1-15 encompass methods of administering the recited amylin or amylin agonist for a period of hours, days, weeks or months. Claims 1-3 encompass administration of any amylin or amylin agonist by any route, in any quantity and any number of times per day to any human subject for any length of time. It is further noted that the limitation "treating" obesity is defined in the instant specification to include "controlling weight for cosmetic purposes in humans, that is to control body weight to improve bodily appearance", or preventing "the onset of symptoms or complications, alleviating the symptoms or complications". See last paragraph on page 12.

It is noted that the instant specification does not provide a definition for the limitation "preventing obesity" indicating how "treating obesity" differs from "preventing obesity", or whether the limitations, "treating" and "preventing" have a synonymous meaning in connection with obesity.

The specification at page 10 characterizes 'increased appetite' as a sign strongly associated with obesity (see second paragraph). Thus, increased appetite, and therefore, increased food intake, are symptoms of obesity.

It is further noted that one of the parameters described in the instant specification to determine amylin agonistic activity is inhibition or delaying of gastric emptying (see second paragraph on page 19; and Examples 9 and 10). The Office views inhibition or delaying of gastric emptying as an inherent amylin agonistic, body-weight reducing function of amylin or amylin agonist or amylin agonist analogue.

Thompson *et al.* (April, 1997) teach a method of treating human subjects with IDDM or

type 1 diabetes who are on insulin by administering, subcutaneously, 30 or 100 micrograms (which falls in the dose range recited in claim 6) q.i.d. of pramlintide, an amylin agonist analogue which "incorporates proline substitutions at positions 25, 28 and 29 of the amylin molecule" (see abstract; and page 632). The method induced a dose-dependent **anorexia** and nausea in pramlintide-treated patients at 30 micrograms and 100 micrograms doses respectively (see page 635, left column). Thompson *et al.* (April, 1997) teach the modulation of gastric emptying to be responsible, at least in part, for the reduction of glucose concentrations effected by pramlintide, consistent with the art-reported slowed glucose absorption and reduction in postprandial plasma glucose concentrations resulting from slowing of gastric emptying of liquids and solids in patients with IDDM induced by intravenous infusions of pramlintide (see page 636, left column). That the anorexic and gastric emptying-slowing effects of pramlintide in the prior art method necessarily result in therapeutic weight loss in the subjects treated is inherent from the teachings of the prior art, since therapeutic agents with these effects have been successfully used in the art as anti-obesity agents in the treatment of obesity or weight gain. For instance, Guthrie *et al.* taught the treatment of obesity in mammals with the use of anorectic agents that delay gastric emptying (see abstract; and column 2, lines 25-28). Guthrie *et al.* taught that agents exhibiting potent anorectic, i.e., appetite suppressant, activity in mammals are useful in the treatment of obesity (see column 13, last paragraph).

The teachings of Thompson *et al.* (April, 1997) anticipate the instant claims. Guthrie *et al.* is **not** used as a secondary reference in combination with Thompson *et al.* (April, 1997), but rather is used to show that every element of the claimed subject matter is disclosed by Thompson *et al.* (April, 1997). See *In re Samour* 197 USPQ 1 (CCPA 1978).

Claims 1-6 and 11-15 are anticipated by Thompson *et al.* (April, 1997).

26) Claims 1-6 and 11-15 are rejected under 35 U.S.C. § 102(b) as being anticipated by Kolterman *et al.* (*Diabetologia* 39: 492-499, April, 1996, already of record) (Kolterman *et al.*, 1996) in light of *The Random House Dictionary* (Ed. Flexner *et al.*, Random House, page 32, New York, 1984).

It is noted that the method claimed in claims 1-6 encompass both insulin-taking and non-insulin-taking human subjects. The methods of claims 1-5 and 11-15 do not require that a

specific amount of the recited amylin or amylin agonist be administered. The methods of claims 1-3 and 11-15 do not require that the recited amylin or amylin agonist be administered via a specific route. Claims 1-15 encompass methods of administering the recited amylin or amylin agonist for a period of hours, days, weeks or months.

It is further noted that the limitation "treating obesity" is defined in the instant specification to include "controlling weight for cosmetic purposes in humans, that is to control body weight to improve bodily appearance", or preventing "the onset of symptoms or complications, alleviating the symptoms or complications". See last paragraph on page 12.

It is noted that the instant specification does not provide a definition for the limitation "preventing obesity" indicating how "treating obesity" differs from "preventing obesity", or whether the limitations, "treating" and "preventing" are synonymous with regard to obesity.

The specification at page 10 characterizes 'increased appetite' and preference for highly caloric food as signs strongly associated with obesity (see second paragraph). Thus, increased appetite and therefore, increased food intake are symptoms of obesity.

One of the parameters described in the instant specification to determine amylin agonistic activity is inhibition or delaying of gastric emptying (see second paragraph on page 19; and Examples 9 and 10). Inhibition or delaying of gastric emptying is viewed as an inherent amylin agonistic, anti-obesity function of amylin, amylin agonist or amylin agonist analogue.

Kolterman *et al.* (1996) teach a method of subcutaneous administration of 30, 100 or 300 μg of pramlintide or AC137 (i.e., ^{25,28,29}pro-h-amylin), a human amylin analogue, to human patients with insulin-dependent diabetes mellitus or IDDM who are on insulin. Pramlintide is administered three times daily for a period of 14 days (see abstract; and page 493). Kolterman *et al.* (1996) discuss the art-reported accelerated gastric emptying in IDDM patients (see page 498). The pramlintide administration to insulin-taking IDDM patients induced **anorexia**, recurrent nausea and significant reduction in postprandial hyperglycemia (see paragraph bridging left and right columns on page 497; and third full paragraph, right column on page 498). It is taught that amylin exerts a potent effect which slows gastric emptying in man and can reduce postprandial plasma glucose excursions (see page 493). Kolterman *et al.* (1996) discuss the art-reported, accelerated gastric emptying in IDDM patients and suggest that the effect of pramlintide on

postprandial plasma glucose concentrations may be predominantly mediated via effects upon gastric emptying (see page 498).

It is noted that the term "anorexia" is defined in '*The Random House Dictionary*' as 'abnormal lack of appetite' (see the attached sheets).

That the prior art method necessarily serves as a method of treating obesity, i.e., "controlling weight for cosmetic purposes in humans, that is to control body weight to improve bodily appearance", or preventing the "onset of symptoms or complications, alleviating the symptoms or complications", is inherent from the teachings of Kolterman *et al.* (1996). By inducing anorexia and recurrent nausea, pramlintide used in Kolterman's method necessarily causes abnormal lack of appetite, thereby decreasing if not inhibiting, the food intake, or the quantity or frequency of food intake, which in turn controls the body weight of the patients for cosmetic purposes or improves the bodily appearance of the patients administered with pramlintide.

Claims 1-6 and 11-15 are anticipated by Kolterman *et al.* (Kolterman *et al.*, 1996).

27) Claims 1-6 and 11-15 are rejected under 35 U.S.C § 102(b) as being anticipated by Kolterman *et al.* (WO 95/07098) ('098).

It is noted that the instant specification defines "treating" as follows (see page 12):

> ..... the management and care of a patient for the purpose of combating the disease, condition or disorder, and includes the administration of an amylin or an amylin agonist to prevent the onset of symptoms or complications, alleviating the symptoms or complications, or eliminating the disease condition or disorder. Treating obesity therefor includes the inhibition of weight gain and inducing weight loss in patients in need thereof. Additionally, treating obesity is meant to include **controlling weight for cosmetic purposes in humans**, that is **to control body weight to improve bodily appearance**. [Emphasis added].

Kolterman *et al.* ('098) teach a method comprising administering a therapeutically effective amount of an amylin, amylin agonist or amylin agonist analogue, such as, ^{25,28,29}pro-h-amylin or AC-0137 or tripro-amylin. The method results in reduction in post-prandial glucose levels and delaying of gastric emptying. Human IDDM patients on insulin therapy were administered intravenously or subcutaneously with 30, 100 or 300 micrograms of tripro-amylin three times a day for 14 days (see claims 1-3, 19 and 23-26; page 44, last paragraph through page 46, first full paragraph; pages 38 and 39; the full paragraph on page 37; page 21; Figure 11-13

and Examples 2-4). That the prior art method serves necessarily as a method of treating obesity or controlling body weight is inherent from the teachings of Kolterman *et al.* ('098). The Kolterman's ('098) method meets the instantly claimed method with regard to the composition used, the dose and frequency of the composition used, and the subject species (human) to whom the composition is administered. Therefore, the prior art method inherently and necessarily brings about the same therapeutic effects brought about by the Applicants' method, i.e., controlling weight for cosmetic purposes, or controlling body weight to improve bodily appearance in humans.

Claims 1-6 and 11-15 are anticipated by Kolterman *et al.* ('098).

Rejection(s) under 35 U.S.C. § 103

28) Claims 1-6 and 11-15 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Kolterman *et al.* (*Diabetologia* 39: 492-499, April 1996, already of record) (Kolterman *et al.*, 1996) in view of Robert *et al.* (WO 91/16917).

It is noted that the instant specification defines "treating" as follows (see page 12):

> ..... the management and care of a patient for the purpose of combating the disease, condition or disorder, and includes the administration of an amylin or an amylin agonist to prevent the onset of symptoms or complications, alleviating the symptoms or complications, or eliminating the disease condition or disorder. Treating obesity therefor includes the inhibition of weight gain and inducing weight loss in patients in need thereof. Additionally, treating obesity is meant to include **controlling weight for cosmetic purposes in humans, that is to control body weight to improve bodily appearance.** [Emphasis added].

It is noted that the method claimed in claims 1-6 encompass both insulin-taking and non-insulin-taking human subjects. The methods of claims 1-5 and 11-15 do not require that a specific amount of the recited amylin or amylin agonist be administered. The methods of claims 1-3 and 11-15 do not require that the recited amylin or amylin agonist be administered via a specific route. Claims 1-6 and 11-15 encompass methods of administering the recited amylin or amylin agonist for a period of hours, days, weeks or months.

It is further noted that the limitation "treating obesity"is defined in the instant specification to include "controlling weight for cosmetic purposes in humans, that is to control body weight to improve bodily appearance", or preventing "the onset of symptoms or complications, alleviating the symptoms or complications". See page 12 of the instant

specification.

The specification at page 10 characterizes 'increased appetite' as a sign strongly associated with obesity. Thus, increased appetite or increased food intake is a symptom of obesity and plays an important role in obesity.

One of the parameters described in the instant specification to determine amylin agonistic activity is inhibition or delaying of gastric emptying (see page 19; and Examples 9 and 10). Inhibition or delaying of gastric emptying is viewed as an inherent, amylin agonistic, anti-obesity function of pramlintide.

The teachings of Kolterman *et al.* (1996) are explained above. Although Kolterman *et al.* (1996) are silent about the body weight of the human subjects following pramlintide treatment, it is implicit from Kolterman's (1996) teaching that their method necessarily served as a method of treating obesity or inducing weight loss, i.e., a method that 'controls body weight' for cosmetic purposes, or improves bodily appearance as defined in the instant specification, in light of what is known in the art. By significantly delaying/restoring gastric emptying in the treated patients, the pramlintide used in Kolterman's (1996) method necessarily induced weight-controlling or weight-reducing effects, since it is well known in the art that anti-gastric emptying agents also serve as weight-reducing agents. For instance, Robert *et al.* demonstrated that a gastric emptying-retarding compound also served as an anti-obesity agent by retaining the food in the stomach of the treated individuals for prolonged periods of time, thus causing no desire to eat, thereby causing weight loss. See page 2, lines 24-26 of Robert *et al.* Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made that Kolterman's (1996) method also served as a method of treating obesity, i.e., a method of "controlling weight for cosmetic purposes in humans, that is to control body weight to improve bodily appearance", or preventing or alleviating the onset of the symptom of increased appetite or food intake.

Claims 1-6 and 11-15 are *prima facie* obvious over the prior art of record.

29) Claims 1-6 and 11-15 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Kolterman *et al.* (*Diabetologia* 39: 492-499, April, 1996, already of record) (Kolterman *et al.*, 1996) or Kolterman *et al.* (WO 95/07098) ('098) in view of Frishman *et al.* (*In*: *Cardiovascular*

Pharmacotherapeutics. (Eds) Frishman WH *et al.* McGraw-Hill Health Professions Division, New York, Chapter 48, pages 1093-1114, February 1997), or Weintraub *et al.* (*Nutrition Rev.* 49: 237-249, 1989).

It is noted that the instant specification defines "treating" as follows (see page 12):

> ..... the management and care of a patient for the purpose of combating the disease, condition or disorder, and includes the administration of an amylin or an amylin agonist to prevent the onset of symptoms or complications, alleviating the symptoms or complications, or eliminating the disease condition or disorder. Treating obesity therefor includes the inhibition of weight gain and inducing weight loss in patients in need thereof. Additionally, treating obesity is meant to include **controlling weight for cosmetic purposes in humans**, that is **to control body weight to improve bodily appearance**. [Emphasis added].

The teachings of Kolterman *et al.* (1996) or Kolterman *et al.* ('098) have been explained above, which are silent about the control of body weight of the human subjects following treatment with pramlintide, i.e, an amylin species, and therefore silent about the use of their method for treating obesity, i.e., to control body weight for cosmetic purposes, or to improve bodily appearance.

However, Frishman *et al.* taught amylin to have anorectic effect (see page 1106, right column, last paragraph). Frishman *et al.* expressly taught the use of peripherally acting amylin as one of the innovative strategies to treat obesity (see Table 48-3). It is further taught that the administration of amylin both centrally and peripherally reduces food intake. Frishman *et al.* also taught that amylin was equally effective in decreasing feeding in ob/ob and db/db mice (see page 1107, left column, lines 1 and 2).

Weintraub *et al.* expressly teach, slowing of gastric emptying by increasing gastric distension to inhibit food intake, as an approach for treating obesity (see title; and page 43, left column, second full paragraph).

Given that Kolterman's (1996) method induces both anorexia and delay in gastric emptying in human patients, or given that Kolterman's ('098) method results in delaying of gastric emptying, it would have been obvious to one of ordinary skill in the art at the time the invention was made to use Kolterman's (1996 or '098) method of subcutaneous administration of pramlintide for treating obesity, i.e., controlling body weight for cosmetic purposes, or controlling body weight to improve bodily appearance, to produce the instant invention, with a

reasonable expectation of success. One skilled in the art would have been motivated to produce the instant invention for the expected benefit of using Kolterman's (1996 or '098) method, not only to treat IDDM; but advantageously, for treating obesity as well, by making use of the anorectic and/or the anti-gastric emptying properties of Kolterman's (1996 or '098) pramlintide, since Frishman *et al.* expressly provides the motivation by teaching the use of peripherally acting amylin as one of the innovative strategies to treat obesity, or since Weintraub *et al.* expressly teach slowing of gastric emptying as an approach for treating obesity.

Claims 1-6 and 11-15 are *prima facie* obvious over the prior art of record.

30) Claims 1-3 and 11-15 are rejected under 35 U.S.C § 103(a) as being unpatentable over Kong *et al.* (*Diabetologia* 40: 82-88, January 1997, Applicants' IDS) (Kong *et al.*, 1997), or MacDonald *et al.* (*Diabetologia* 38: Suppl. 1, A118, August 1995, Applicants' IDS) in view of Robert *et al.* (WO 91/16917), Jonderko *et al.* (*Aliment. Pharmacol. Ther.* 5: 413-418, 1991) (Jonderko *et al.*, 1991) and Frishman *et al.* (*In*: *Cardiovascular Pharmacotherapeutics*. (Eds) Frishman WH *et al.* McGraw-Hill Health Professions Division, New York, Chapter 48, pages 1093-1114, February 1997), or Morley *et al.* (*Pharmacol. Biochem. Behav.* 44: 577-580, 1993) (Morley *et al.*, 1993).

The teachings of MacDonald *et al.* are explained above.

Kong *et al.* (1997) teach a method of intravenous infusion of 125 micrograms (i.e., an effective amount) of pramlintide, an amylin species, to human subjects with IDDM or type 1 diabetes mellitus. The method delayed gastric emptying so much that t50 values could not be calculated for solid or liquid meal components (see abstract; page 85 and Figure 3). Kong *et al.* (1997) teach that faster rates of gastric emptying have been reported in humans with IDDM and that slowing the rate of gastroenteritis in these patients might prove beneficial in improving glycaemic control. Kong *et al.* (1997) conclude that amylin or an amylin agonist may be useful in modifying gastric emptying. Kong *et al.* (1997) specifically recommend amylin or amylin agonist for IDDM or type 1 patients having rapid gastric emptying (see page 87, right column). Although Kong *et al.* (1997) or MacDonald *et al.* are silent about the change in body weight of the human subjects following pramlintide treatment, it is implicit from Kong's (1997) or MacDonald's teaching that their method necessarily served as a method of treating obesity or

inducing weight loss, i.e., a method of 'controlling body weight' for cosmetic purposes, or improving bodily appearance, in light of what is known in the art.

It was known in the art that gastric emptying-retarding compounds also serve as anti-obesity agents. For instance, Robert *et al.* demonstrated that a gastric emptying-retarding compound also served as an anti-obesity agent by retaining the food in the stomach of the treated individuals for prolonged periods of time, thus causing no desire to eat, thereby causing weight loss. See page 2, lines 24-26 of Robert *et al.*

Frishman *et al.* taught amylin to have anorectic effect (see page 1106, right column, last paragraph). Frishman *et al.* expressly taught the use of peripherally acting amylin as one of the innovative strategies to treat obesity (see Table 48-3). It is taught that the administration of amylin both centrally and peripherally reduces food intake. Frishman *et al.* also taught that amylin was equally effective in decreasing feeding in ob/ob and db/db mice (see page 1107, left column, lines 1 and 2).

Similarly, Morley *et al.* (1993) showed that amylin is a peripheral anorectic peptide. Morley *et al.* (1993) taught that administration of amylin to a mammal decreased or suppressed food intake (see abstract).

Jonderko *et al.* (1991) teach that gastric emptying rate influences the feeling of satiety. Jonderko *et al.* expressly teach that the combination of an anorectic effect with the inhibition of gastric emptying can be considered a desirable feature of an anti-obesity agent (see page 416, first sentence under 'Discussion').

Given the art-demonstrated anti-gastric emptying function and the peripheral anorectic function of amylin as taught by Kong *et al.* (1997) and Frishman *et al.* or Morley *et al.* respectively, it would have been obvious to one of ordinary skill in the art at the time the invention was made to use Kong's (1997) or MacDonald's method of administration of pramlintide for treating obesity, i.e., controlling body weight for cosmetic purposes, or controlling body weight to improve bodily appearance, to produce the instant invention, with a reasonable expectation of success, because Robert *et al.* expressly taught that a gastric emptying-retarding compound also served as an anti-obesity agent by retaining the food in the stomach of the treated individuals for prolonged periods of time, thus causing no desire to eat, thereby

causing weight loss. One skilled in the art would have been motivated to produce the instant invention for the expected benefit of using Kong's (1997) or MacDonald's method, not only to treat IDDM, but advantageously, for treating obesity as well by making use of the anorectic and anti-gastric emptying properties of Kong's (1997) or MacDonald's amylin species, since amylin, advantageously, possesses the combination of the anorectic and the anti-gastric emptying properties, the two properties desirable in an anti-obesity agent as taught by Jonderko *et al.* (1991).

Claims 1-3 and 11-15 are *prima facie* obvious over the prior art of record.

31) Claims 1-6 and 11-15 are rejected under 35 U.S.C § 103(a) as being unpatentable over Kolterman *et al.* (WO 95/07098) ('098) or Kolterman *et al.* (*Diabetologia* 39: 492-499, April, 1996, already of record) (Kolterman *et al.*, 1996) in view of Morley *et al.* (*Pharmacol. Biochem. Behav.* 44: 577-580, 1993) (Morley *et al.*, 1993) and Jonderko *et al.* (*Aliment. Pharmacol. Ther.* 5: 413-418, 1991) (Jonderko *et al.*, 1991).

It is noted that the instant specification defines "treating" as follows (see page 12):

> ..... the management and care of a patient for the purpose of combating the disease, condition or disorder, and includes the administration of an amylin or an amylin agonist to prevent the onset of symptoms or complications, **alleviating the symptoms** or **complications**, or eliminating the disease condition or disorder. Treating obesity therefor includes the inhibition of weight gain and inducing weight loss in patients in need thereof. Additionally, treating obesity is meant to include **controlling weight for cosmetic purposes in humans**, that is **to control body weight to improve bodily appearance**. [Emphasis added].

Kolterman *et al.* ('098) teach a method comprising administering a therapeutically effective amount of an amylin, amylin agonist or amylin agonist analogue, such as, ^{25,28,29}pro-h-amylin or AC-0137 or tripro-amylin. The method results in reductio in post-prandial glucose levels and delaying of gastric emptying. Human IDDM patients, who were on insulin therapy, were administered intravenously or subcutaneously with 30, 100 or 300 micrograms of tripro-amylin three times a day for 14 days (see claims 1-3, 19 and 23-26; page 44, last paragraph through page 46, fist full paragraph; page 38 and 39; the full paragraph on page 37; page 21; Figure 11-13 and Examples 2-4).

Kolterman *et al.* (1996) teach a method of subcutaneous administration of 30, 100 or 300 μg of pramlintide or AC137 (i.e., ^{25,28,29}pro-h-amylin), a human amylin analogue, to human

patients with insulin-dependent diabetes mellitus or IDDM who are on insulin. Pramlintide is administered three times daily for a period of 14 days (see abstract; and page 493). This pramlintide administration to insulin-taking IDDM patients induced **anorexia**, recurrent nausea and significant reduction in postprandial hyperglycemia (see paragraph bridging left and right columns on page 497; and third full paragraph, right column on page 498). It is taught that amylin exerts a potent effect which slows gastric emptying in man and can reduce postprandial plasma glucose excursions (see page 493). Kolterman *et al.* (1996) discuss the art-reported accelerated gastric emptying in IDDM patients and suggest that the effect of pramlintide on postprandial plasma glucose concentrations may be predominantly mediated via effects upon gastric emptying (see page 498).

Although Kolterman *et al.* ('098 or 1996) do not expressly teach that their method of administration to a human subject, 30, 100 or 300 micrograms of amylin or an amylin agonist such as ^{25,28,29}pro-h-amylin, or an amylin agonist analogue subcutaneously 1-3 times per day treats human obesity, it is implicit that Kolterman's ('098 or 1996) method serves as a method of treating obesity in light of what is well known in the art.

For instance, Jonderko *et al.* (1991) teach that gastric emptying rate influences the feeling of satiety. Jonderko *et al.* expressly teach that the combination of an anorectic effect with the inhibition of gastric emptying can be considered a desirable feature of an anti-obesity agent (see page 416, first sentence under 'Discussion').

Morley *et al.* (1993) showed that amylin is a peripheral anorectic peptide. Morley *et al.* (1993) teach that administration of amylin to a mammal decreased or suppressed food intake (see abstract).

Since amylin is an art-known anorectic agent as taught by Morley *et al.* (1993) and an anti-gastric emptying agent as demonstrated by Kolterman *et al.* ('098 or 1996), it would have been obvious to one of ordinary skill in the art at the time the invention was made to use Kolterman's ('098 or 1996) method of administering to a human subject a composition comprising amylin, an amylin agonist analogue, or an amylin agonist compound, such as, ^{25,28,29}pro-h-amylin, for treating human obesity to produce the instantly claimed method, with a reasonable expectation of success. Since the combination of an anorectic effect and the

inhibition of gastric emptying is taught in the art to be a desirable feature in an anti-obesity agent as taught by Jonderko *et al.* (1991), one skilled in the art would have been motivated to produce the instant invention for the expected benefit of treating obesity in humans, as treatment of human obesity is highly desired in the art. Because the amylin used in Kolterman's ('098 or 1996) method beneficially or desirably exerts both an anorectic effect and an anti-gastric emptying effect as taught by Morley *et al.* (1993) and Jonderko *et al.* (1991) respectively, Kolterman's ('098 or 1996) amylin would have been expected to serve effectively as a therapeutic anti-obesity agent in the prior art method. Those skilled in the art would have understood that Kolterman's ('098 or 1996) method of delaying gastric emptying by amylin administration would have also served as a method of treating obesity. Kolterman's ('098 or 1996) method is viewed as a method that improves bodily appearance and 'controls body weight' for cosmetic purposes.

Claims 1-6 and 11-15 are *prima facie* obvious over the prior art of record.

32) Claims 1-6 and 11-15 are rejected under 35 U.S.C § 103(a) as being unpatentable over Kolterman *et al.* (WO 95/07098) (Kolterman *et al.*, '098) or Kolterman *et al.* (*Diabetologia* 39: 492-499, April 1996, already of record) (Kolterman *et al.*, 1996) in view of Frishman *et al.* [*In*: *Cardiovascular Pharmacotherapeutics*. (Eds) Frishman WH *et al.* McGraw-Hill Health Professions Division, New York, Chapter 48, pages 1093-1114, February 1997] and Jonderko *et al.* (*Israel J. Med. Sci.* 25: 20-24, 1989) (Jonderko *et al.*, 1989) or Guthrie *et al.* (US 4,443,619).

The disclosure of Kolterman *et al.* ('098 or 1996) has been explained above. A *Graham v. John Deere* factual inquiry indicates that Kolterman *et al.* ('098 or 1996) are silent about their method of administration to a human subject, 30, 100 or 300 micrograms of amylin or an amylin agonist such as ^{25,28,29}pro-h-amylin, or an amylin agonist analogue intravenously or subcutaneously, 1-3 times per day, treats human obesity. However, it is implicit that Kolterman's ('098 or 1996) method serves as a method of treating obesity in light of what is well known in the art.

However, Frishman *et al.* teach the use of peripherally acting amylin as one of the innovative strategies to treat obesity (see Table 48-3). The administration of amylin both centrally and peripherally reduces food intake. Amylin is taught to have anorectic effect (see

page 1106, right column, last paragraph). Frishman *et al.* teach that amylin was equally effective in decreasing feeding in ob/ob and db/db mice (see page 1107, left column, lines 1 and 2).

Jonderko *et al.* (1989) expressly suggest that anorectic agents that delay GE or gastric emptying might contribute to progress in the treatment of obesity (see the last sentence in the paragraph bridging pages 22 and 23).

Similarly, Guthrie *et al.* teach that agents exhibiting potent anorectic or appetite suppressant activity in mammals are useful in the treatment of obesity (see column 13, last paragraph). Guthrie *et al.* teach the use of anorectic agents that delay gastric emptying for the treatment of obesity in mammals (see abstract; and column 2, lines 25-28).

Given that amylin is an art-known peripherally acting anorectic agent, which is known to reduce food intake in mammals as taught by Frishman *et al.* and an anti-gastric emptying and/or anorectic agent as demonstrated by Kolterman *et al.* ('098 or 1996), it would have been obvious to one of ordinary skill in the art at the time the invention was made to use Kolterman's ('098 or 1996) method of administering an amylin, an amylin agonist analogue, or an amylin agonist compound, such as, ^{25,28,29}pro-h-amylin, to a human subject for treating obesity to produce the instantly claimed method, with a reasonable expectation of success. Since anorectic agents that delay gastric emptying are suggested in the art for the treatment of obesity as taught by Jonderko *et al.* (1989) or Guthrie *et al.*, one skilled in the art would have been motivated to produce the instant invention for the expected benefit of treating obesity in humans, as treating human obesity or controlling human body weight is highly desired in the art. Given the knowledge in the art, one skilled in the art would have readily understood that the anti-gastric emptying amylin used in Kolterman's ('098 or 1996) method beneficially or desirably also exerts an anorectic effect as taught by Frishman *et al.* and that Kolterman's ('098 or 1996) amylin would have been expected to serve effectively as a therapeutic anti-obesity agent in the prior art method. Those skilled in the art would have understood that Kolterman's ('098 or 1996) method of delaying gastric emptying by the administration of anorectic amylin would have also served as a method of treating obesity, because Jonderko *et al.* (1989) or Guthrie *et al.* explicitly teach or suggest that anorectic or appetite-suppressing agents that delay gastric emptying are also useful in the treatment of obesity.

Claims 1-6 and 11-15 are *prima facie* obvious over the prior art of record.

Remarks

33) Claims 1-15 stand rejected.

34) The prior art made of record and not currently relied upon in any of the rejections is considered pertinent to Applicants' disclosure:

- Frank *et al.* (*Gastroenterology* 109: 755-765, 1995) teach that gastric emptying of liquids is significantly accelerated in type II diabetes mellitus (see abstract).

- Beaumont *et al.* (US 5,321,008) disclose a method comprising administering a therapeutically effective amount of calcitonin, with or without amylin (see abstract; and column 4, third full paragraph). Calcitonin in an amylin agonist (see column 3, lines 34 and 35 and column 7, third full paragraph). The method is used for treatment of type 1 and type 2 diabetes in humans and other insulin-requiring states (see last two lines in column 4). The therapeutic regimen can be 100 micrograms of amylin alone, or 100 micrograms of calcitonin alone (see column 9, second full paragraph and Table 3). Administration of amylin or calcitonin composition in solution is by subcutaneous route in a pharmaceutically acceptable form (see under 'Composition' in column 12). The subcutaneous administration is in an insulin-requiring human (see column 7, lines 11-14). The method is also effective in achieving improved glycemic control over insulin therapy (see column 3). The therapeutic dosage given varies from 0.1 to 1.0 micrograms and is administered in one or multiple doses (see column 13, first full paragraph).

- Tosetti *et al.* (*Inter. J. Obesity* 20: 200-205, 1996) taught that obese subjects had accelerated gastric emptying compared to healthy controls, whereas patients treated for the condition showed slowing of gastric emptying and also a significant decrease of body weight. Tosetti *et al.* teach that gastric emptying, food intake and body weight are integrated parameters in subjects with morbid obesity (see abstract). Tosetti *et al.* expressly teach that the decrease of body weight is associated with a normalization of gastric emptying rates.

- Klein *et al.* (US 5,498,424) teach the use of anorexigenic agents in treating obesity and also advantageously assisting non-obese persons in losing weight (see abstract).

- Thompson *et al.* (*Diabetes* 44: Suppl. 1, 127A, 469, May 1995 - already of record)

teach a method of administration of 100 micrograms of human amylin analogue, AC137, to type II diabetes patients on insulin, which induced nausea in more than 50% of treated patients (see abstract).

- Cooper *et al.* (US 5,124,314 - already of record) suggest amylin to be of clinical utility as an appetite suppressant (see sixth paragraph in column 1).
- Balasubramaniam *et al.* (*Peptides* 12: 919-924, 1991) teach the anorectic effects of and inhibition of food intake by human amylin (see entire document).
- Kolterman *et al.* (*Diabetologia* 39: 492-499, April, 1996 - already of record) (Kolterman *et al.*, 1996) acknowledge that based on genetic work, some skilled in the art have referred to amylin as either 'amylin' or 'IAPP' (see page 492, right column).
- Kong *et al.* (*Diabetes* 46: Suppl. 1: 154A, 1997) teach the subcutaneous administration of a single dose of 30, 60 or 90 micrograms of pramlintide in humans with IDDM or type 1 diabetes mellitus on insulin therapy. All three doses of pramlintide delayed gastric emptying of the solid component of the first meal (see abstract).
- Brown *et al.* (*Diabetes* 43: Suppl. 1, 172A, 1994) by their studies in beagle dogs, taught that amylin, at plasma concentrations near the physiologic range, may play a role in hormonal regulation of gastric emptying (see abstract).
- Clementi *et al.* (*Experientia* 52: 677-679, 1996) taught that different doses of rat amylin injected centrally or peripherally decreased gastric emptying and intestinal transit in rats. Clementi *et al.* taught that subcutaneous administration of 25, 50 or 100 micrograms per kg of amylin dose-dependent effects (see abstract; Figure 3 and page 679).
- Aquino *et al.* (WO 95/28419 and US 5,739,129) disclosed the use of anorectic agents for treating obesity as well as related pathologies, such as, diabetes or hypertension (see entire document).
- Young *et al.* from Amylin Pharmaceuticals Inc., (*Diabetologia* 38: 642-648, 1995) showed that subcutaneous injection of rat amylin dose-dependently inhibited gastric emptying in both normal and diabetic rats (see page 643). Young *et al.* discuss a prior art study which shows that gastric emptying is accelerated in an animal model of IDDM, a condition of amylin deficiency. Exogenous amylin is taught to potently and dose-dependently inhibit gastric

emptying (see page 647).

- Brown *et al.* (*Diabetes* 43: Suppl. 1: 172A, 1994) demonstrated that gastric emptying is slowed by amylin administration in dogs (see abstract).

- Phillips *et al.* (US 5,187,154) expressly teach a method useful in prophylactic treatment of the obese individuals by delaying or inhibiting gastric emptying (see abstract). Phillips *et al.* teach that delaying gastric emptying appears to slow delivery of glucose to the duodenum which reduces postprondial hyperglycemia. Phillips *et al.* teach that in delaying gastric emptying, a treatment is provided to control the development or at least delay the onset of symptoms that are frequently associated with the onset of or have a tendency to develop diabetes mellitus (see abstract; and column 4, first full paragraph).

- Newgard *et al.* (US 6,110,707, filed 17 January 1997) expressly teach a method of providing amylin to a mammal (i.e., inclusive of humans) exhibiting obesity. Newgard *et al.* expressly teach a method of providing amylin to a mammal (i.e., inclusive of humans) exhibiting gastric emptying (see column 4, lines 41-44). Cells encoding amylin are administered to the mammal intraperitoneally or subcutaneously (see column 4, lines 50-52). Newgard *et al.* disclose that amylins may be used in the treatment of obesity (see column 38, lines 2-5).

- Edwards *et al.* (*Life Sci.* 51: 1819-1912, 1992) teach that amylin produces anorexia and that amylin is much mor effective in decreasing food intake when given peripherally than centrally. Edwards *et al.* state that Morley and Flood (*American J. Med.* 81: 679-695, 1986) have demonstrated that amylin decreases food intake in both normal and diabetic mice following parenteral administration. Edwards *et al.* teach that amylin is more effective in reducing food intake in diabetic animals than in non-diabetic animals (see page 1908, under 'Anorexia'). Anorexia is taught to be another effect of amylin (see last paragraph on page 1908).

- Wright *et al.* (*Gastroenterology* 84: 747-751, 1986) expressly teach that the rate of solid gastric emptying in the obese subjects is abnormally rapid. Wright *et al.* further teach that obese subjects were found to have a more rapid emptying rate than non-obese subjects and that obese men were found to empty much more rapidly than their nonobese counterparts (see abstract).

- Cooper *et al.* (*Biochim. Biophys. Acta* 1014: 247-258, 1989, already of record)

teach that NIDDM is associated with obesity in more than 65% of patients suggesting the possibility that this type of diabetes may be due to a disordered mechanism of appetite regulation or energy expenditure (see the sentence bridging pages 255 and 256).

- Carty *et al.* (WO 9637612 and US 6,187,991) disclose a recombinant DNA expressing islet amyloid polypeptide (IAPP) to develop products for use in treatment of obesity and diabetes (see title and abstract).

- Keown *et al.* (US 5,498,424) teach that most pharmacological approaches to the treatment of obesity and methods of weight loss primarily focus on lowering the energy intake of the obese patient and resort to anorectic drugs that modify the metabolism involved in appetite regulation (see column 2, lines 31-36). Keown *et al.* teach that anorexigenic agents are advantageously used to also assist non-obese persons in losing weight (see abstract).

- De Luca *et al.* (US 4,960,759) teach that intravenous infusion of CCK reduces food intake both in obese and lean human subjects. De Luca *et al.* teach that cholecystokinin (CCK) produces decrease of gastric emptying (see column 1, lines fourth full paragraph).

- Hunt *et al.* (*Gastroenterology* 84: 747-751, 1983) teach that obese subjects have an abnormally rapid rate of gastric emptying compared to non-obese subjects (see abstract), whereas obese subjects who were able to lose wight did not show significant change in the rates of gastric emptying of solids or liquids (see paragraph bridging left and right columns on page 749). Hunt *et al.* taught that as discussed in the prior art by others, "rapid emptying is a predisposing factor in the genesis of increased food intake and obesity". Hunt *et al.* expressly taught that the "fact that the obese subjects who were able to lose weight effectively have intermediate solid gastric emptying rates" supports the concept.

- Guthrie *et al.* (US 4,443,619) teach the use of anorectic agents that delay gastric emptying for the treatment of obesity in mammals (see abstract; and column 2, lines 25-28). Guthrie *et al.* teach that agents exhibiting potent anorectic or appetite suppressant activity in mammals are useful in the treatment of obesity (see column 13, last paragraph).

- More than a year prior to the effective filing date of the instant invention, Young *et al.* from Amylin Pharmaceuticals, (*Drug Development Res.* 37: 231-248, July 1996, already of record) taught that amylin is absent or reduced in individuals with type I diabetes mellitus **and**

"in many insulin-treated patients with type II diabetes". Young *et al.* taught that amylin replacement therapy may be beneficial in amylin-deficient individuals, such as, those with type I diabetes mellitus and with insulin-requiring type II diabetes mellitus (see abstract; and page 231). Among multiple potent actions of exogenously administered amylin, such as, pramlintide, reduction f postprandial hyperglycemia and inhibition of gastric emptying of solids and liquids in type I diabetic subjects, which is believed to be associated with postprandial glucose-smoothing in humans, are the two. Young *et al.* expressly teach that, in humans, "a striking effect" of the human amylin analogue, pramlintide, is "the reduction of postprondial hyperglycemia" in subjects with type I and insulin-treated type II diabetes mellitus (see page 232, left column).

- It is well known in the art that food intake and obesity are closely associated with each other. For instance:

  - Chen *et al.*(US 5,690,691) teach that in an obese person, food is passed from the stomach into the small intestine at a relatively fast rate, thereby causing the person to feel hungry and that this encourages additional caloric intake beyond that which is necessary for good health. Chen *et al.* further teach that it could be advantageous to prolong the time food is kept in the obese patient's stomach to promote a prolonged "full" feeling and discourage further food intake (see column 8, second full paragraph).

  - Bogentoft *et al.*(US 5,462,742) teach that the serious problem of obesity could be helped by a reduced food intake and that decreasing energy intake causes weight loss in obese subjects. Bogentoft *et al.* teach that slowing gastric emptying results in these effects (see column 1, lines 29-37).

- Kolterman *et al.* (US 6,114,304) teach that surprisingly, amylin, "previously described as a hyperglycemic agent (i.e., one causing elevated glucose) was found instead to decrease post-prandial plasma glucose levels in dogs (see column 16, lines 53-57).

- Kolterman *et al.* (*Diabetologia* 37: Suppl. 1: A72, 278, 1994) teach a method of delaying gastrointestinal absorption of nutrients and reducing postprandial hyperglycemia in humans with juvenile-onset diabetes by intravenous infusion of 30, 100 or 300 micrograms of tri-pro amylin (see abstract).

- Lartey *et al.* (US 5,578,579) teach that "delayed gastric emptying" refers to slow

evacuation of gastric contents into the small intestine not caused by mechanical obstruction of the gastric outlet. Lartey *et al.* teach that intractable nausea and vomiting may lead to significant weight loss (see fourth paragraph in column 5).

- Janes *et al.* (*Diabetes* 45: Suppl.2: A865, p. 235A, 1996, already of record) teach that amylin is deficient is not only in Type I diabetes, but also in some cases of Type II diabetes and therefore, is a candidate for hormone replacement therapy (see abstract).

- Young *et al.* (*Diabetes* 45: Suppl.2: page 187A, A689, 1996) teach that amylin is deficient not only in Type I diabetes, but also in some cases of Type II diabetes (see abstract).

35) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center located in Crystal Mall 1. The transmission of such papers by facsimile must conform with the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The CM1 facsimile center's telephone number is (703) 308-4242, which is able to receive transmissions 24 hours a day and 7 days a week. The RightFax number for submission of before-final amendments is (703) 872-9306. The RightFax number for submission of after-final amendments is (703) 872-9307.

36) Any inquiry concerning this communication or earlier communication(s) from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (703) 308-9347. A message may be left on the Examiner's voice mail service. The Examiner can normally be reached on Monday to Friday from 7.15 a.m to 4.15 p.m. except one day each bi-week which would be disclosed on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

SD
S. DEVI, PH.D.
PRIMARY EXAMINER

May, 2002